General

Guideline Title

The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: update of the 2001 evidence-based review.

Bibliographic Source(s)

American Society for Blood and Marrow Transplantation. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: update of the 2001 evidence-based review. Biol Blood Marrow Transplant. 2011 Jan;17(1):18-9. PubMed

Oliansky DM, Czuczman M, Fisher RI, Irwin FD, Lazarus HM, Omel J, Vose J, Wolff SN, Jones RB, McCarthy PL Jr, Hahn T. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: update of the 2001 evidence-based review. Biol Blood Marrow Transplant. 2011 Jan;17(1):20-47.e30. [93 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Hahn T, Wolff SN, Czuczman M, Fisher RI, Lazarus HM, Vose J, Warren L, Watt R, McCarthy PL Jr. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. Biol Blood Marrow Transplant 2001;7(6):308-31.

Recommendations

Major Recommendations

The levels of evidence (1++ to 4) and the grades of recommendations (A-D) are defined at the end of the "Major Recommendations" field.

The following updated treatment recommendations are offered for the role of stem cell transplantation (SCT) as treatment for diffuse large B cell lymphoma (DLBCL), and are based on consensus reached by an expert panel following a systematic review of the literature published since the 2001 original evidence-based review (EBR).

Autologous SCT versus Non-transplantation Therapy

1. Autologous SCT provides a significant survival benefit and is recommended as part of salvage therapy for patients with chemosensitive relapsed DLBCL. This original recommendation is unchanged, with no new data published since the original EBR. (Grade of Recommendation A, Highest Level of Evidence 1+)

2. Autologous SCT is not recommended for patients who achieve only a partial response to an abbreviated (3 cycles) induction regimen. This original recommendation is unchanged, with no new data published since the original EBR. (Grade of Recommendation A, Highest Level of Evidence 1+)
3. Based on new data published since the original EBR, autologous SCT as first-line therapy is not recommended for any International Prognostic Index group at this time; however, none of the published studies included rituximab in their treatment protocols. Ongoing studies that include rituximab may change this recommendation. (Grade of Recommendation A, Highest Level of Evidence 1++)

Autologous SCT: Timing and Protocol

1. Based on new data published since the original EBR, older age (>60 years), in and of itself, is not a contraindication for autologous SCT as long as other SCT eligibility criteria are met. No upper age limit has been defined. However, SCT outcomes (transplant-related mortality, relapse, survival) in older adults are not as good as in younger adults. (Grade of Recommendation B, Highest Level of Evidence 2+)
2. Based on new data published since the original EBR, autologous SCT using peripheral blood, compared to bone marrow, provides no survival benefit or improved tumor control. However, autologous SCT using peripheral blood is safer and easier to use with faster engraftment and lower rate of death because of infection; hence, peripheral blood is the standard autologous stem cell source. (Grade of Recommendation A, Highest Level of Evidence 1++)
3. Based on new data published since the original EBR, planned tandem, or multiple sequential autologous SCTs are not recommended. (Grade of Recommendation B, Highest Level of Evidence 2+)
4. The new data published since the original EBR are insufficient to recommend routine post-autologous SCT maintenance with rituximab outside of a clinical trial. (No Recommendation, Highest Level of Evidence 1+)
5. The new data published since the original EBR are insufficient to make a treatment recommendation regarding fewer versus more cycles of induction therapy prior to first-line autologous SCT. (No Recommendation, Highest Level of Evidence 2++)

Autologous versus Allogeneic SCT

Based on new data published since the original EBR, there are equivalent survival outcomes after autologous and allogeneic SCT. Neither donor option is recommended over the other because they have competing risks with regard to relapse and transplant related mortality. Comparison of these two techniques is biased by different patient selection criteria. (No Recommendation, Highest Level of Evidence 2++)

Allogeneic SCT: Conditioning

The new data published since the original EBR are insufficient to recommend reduced intensity versus myeloablative conditioning for allogeneic SCT. Based on one study and expert opinion, reduced intensity conditioning (RIC) appears to be an acceptable alternative approach for selected patients who cannot tolerate a myeloablative allogeneic SCT. Longer follow-up is needed to clarify the competing risks of relapse and chronic graft-versus-host disease (cGVHD) and their impact on overall survival (OS) and quality of life. Comparison of these regimen intensities is biased by patient selection criteria which have changed over time. (No Recommendation, Highest Level of Evidence 2+)

Definitions:

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-controlled or cohort studies. High-quality case-controlled or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case controlled or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2-	Case-controlled or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Non-analytic studies (e.g., case reports, case series)
4	Expert opinion

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Diffuse large B cell lymphoma (DLBCL)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Radiation Oncology

Intended Users

Health Care Providers

Health Plans

Physicians

Guideline Objective(s)

- To assemble and critically evaluate all valid, peer-reviewed evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in the therapy of diffuse large B cell lymphoma (DLBCL)
- To provide treatment recommendations based on the available evidence
- To identify discrepancies in study design or methodology among published studies that may impact the quality of the evidence
- To identify areas of needed research

DLBCL Update Objectives

- To provide a summary of recent clinical evidence
- To provide timely treatment recommendations
- To determine if new evidence strengthens or changes treatment recommendations provided in the original DLBCL evidence-based review published in 2001

Target Population

Adult patients with diffuse large B cell lymphoma

Interventions and Practices Considered

1. Autologous stem cell transplantation (SCT) versus non-transplantation therapy
2. Autologous SCT: timing and protocol
3. Autologous versus allogeneic SCT
4. Allogeneic SCT: conditioning

Major Outcomes Considered

- Disease-free, event-free, and overall survival
- Response/remission rates (complete/partial)
- Treatment-related mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Methodology for the Diffuse Large B Cell Lymphoma (DLBCL) Update

PubMed and Medline, the Web sites developed by the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were first searched on June 10, 2008, using the search terms "diffuse large B cell lymphoma" OR "DLBCL" AND "transplant" limited to "human trials," "English language," and a publication date of January 1, 2001, or later. Updated searches were conducted on April 10, 2009, and November 4, 2009. In addition to the online database searches, a manual search of the reference lists of the included articles and relevant reviews published since 2000 was conducted. Papers that were published before January 2001, included fewer than 25 DLBCL patients, or were not peer reviewed were excluded. Also excluded were editorials, letters to the editor, Phase I (dose escalation or dose finding)

studies, reviews, consensus conference papers, practice guidelines, and laboratory studies with no clinical correlates. Unlike the original DLBCL evidence-based review (EBR), abstracts and presentations at national or international meetings were not used for the treatment recommendations in this update for reasons previously described. However, abstracts are included in the "Areas of Needed Research and Ongoing Studies" section for the reader's information. Many of the studies evaluated for inclusion in this DLBCL update presented results for high risk or aggressive lymphoma; therefore, to be included, at least 60% of a study's patients had to have DLBCL, unless the results were stratified by histologic subtype of lymphoma.

Number of Source Documents

207

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-controlled or cohort studies. High-quality case-controlled or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case controlled or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2-	Case-controlled or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Non-analytic studies (e.g., case reports, case series)
4	Expert opinion

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The methodology for updating published evidence-based reviews evaluating the role of blood and marrow transplantation in the treatment of selected diseases was published as an American Society for Blood and Marrow Transplantation (ASBMT) editorial policy statement in *Biology of Blood and Marrow Transplantation* (*BBMT*) in 2009. A grading system for the quality and strength of the evidence and strength of each treatment recommendation was published as an editorial policy statement in *BBMT* in 2005. Criteria used to grade the studies that were included in this update and criteria to grade the treatment recommendations are listed in the "Rating Scheme Used for the Strength of the Evidence" and "Rating Scheme Used for the Strength of the Recommendations," respectively. Study design, including sample size, patient selection criteria,

duration of follow-up, and treatment protocol also were considered in evaluating the studies. Clinical studies are described in the tables with sufficient detail to give a concise summary of study design and patient outcomes. All data in the text and tables were abstracted from the original manuscripts by the first author, and double-checked for accuracy and clarity by two other authors. Some articles contained inconsistencies within the data reported; the data most consistent with the text of the article were included in this review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

In 1999, the American Society for Blood and Marrow Transplantation (ASBMT) began developing systematic evidence-based reviews (EBR) and position statements on the effectiveness of autologous and allogeneic hematopoietic stem cell transplantation (SCT) for specific diseases. In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly at approximately five-year intervals. The same expert panel members associated with the original EBR are invited to participate in the update process as well.

Expert Panel Selection for EBRs

To achieve an appropriate balance, physicians who have extensive clinical experience and published research studies using SCT and other therapies in the treatment of the specific disease of interest are invited to join an independent expert panel that examines the summarized literature and provides subsequent treatment recommendations based on the available evidence. Potential panelists are restricted to U.S.-based institutions for 2 reasons: (1) ease of logistics in convening teleconferences, and (2) differences in the health care systems and health insurance coverage between the United States and other countries (including Canada, Europe, etc.), which may result in different expert recommendations based on considerations of costs and access to care. In addition to clinical and research physicians, at least one third-party payer representative, a patient advocate, and a liaison to the ASBMT Steering Committee are invited to serve on the panel.

Consensus Process for Treatment Recommendations

The Treatment Recommendation Table contains the summary of consensus treatment recommendations made by the expert panel based on the summarized evidence. The consensus process involves a teleconference during which panelists critically discuss the evidence for each section of the review and develop initial treatment recommendations according to specified categories. The information is summarized by the primary authors in the Treatment Recommendations Table and distributed to the panelists for additional review and clarification. Any changes suggested by an individual panelist are circulated for review and approval by all panelists. This iterative process concludes when a final version of the Treatment Recommendations Table is approved by all panelists.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

After the final draft of the review is approved by the disease-specific expert panel, it undergoes peer review and is then approved by the Evidence-Based Review (EBR) Steering Committee and the American Society for Blood and Marrow Transplantation (ASBMT) Executive Committee before submission to the journal for further peer review. Any changes requested during the peer-review process must be reviewed and approved by all the expert panelists.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of hematopoietic stem cell transplantation in the treatment of patients with diffuse large B-cell lymphoma (DLBCL)

Potential Harms

Toxicity related to the treatment

Qualifying Statements

Qualifying Statements

Study Limitations

- The strengths of this updated systematic evidence-based review are the details about each study's design and outcomes conveyed in the summary tables for each major section, and the treatment recommendations made by the diffuse large B cell lymphoma (DLBCL) expert panel. A limitation is the exclusion of non peer-reviewed data. Unpublished data can represent "negative" findings that could lead to publication bias; however, the inclusion of high-quality, peer-reviewed publicly available data was of paramount importance. Except in the Ongoing Studies section, data published in abstract form were not included in this review because of the inadequate details of study design or patient characteristics, making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial difficult.
- A limitation of the DLBCL Evidence-Based Review (EBR) Update is that much of the newly presented data is already obsolete in terms of the current standard of care, stressing the need for more timely updates of the EBRs. For example, an abundance of research on the effectiveness of rituximab prior to autologous SCT has been published since the original DLBCL EBR, but as rituximab is now the current standard of care, these studies are not useful for making treatment recommendations. In addition, the lengthy process of conducting and

reporting clinical research emphasizes the need to identify surrogate endpoints or molecular markers that are predictive of long-term survival in DLBCL patients. Further delineation of clinical risk factors may facilitate appropriate selection of DLBCL patients for autologous versus allogeneic stem cell transplantation (SCT).

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jan

Guideline Developer(s)

American Society for Blood and Marrow Transplantation - Professional Association

Source(s) of Funding

National Marrow Donor Program

Guideline Committee

Diffuse Large B Cell Lymphoma (DLBCL) Expert Panel

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

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Guideline Availability

Electronic copies: A list of American Society for Blood and Marrow Transplantation (ASBMT) documents, along with links to individual position statements and evidence-based reviews, is available from the ASBMT Web site .

Print copies: Available from Theresa Hahn, PhD, Roswell Park Cancer Institute, Medicine, Elm and Carlton Sts, Buffalo, NY 14263 (e-mail: theresa.hahn@roswellpark.org).

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 2, 2011. The information was verified by the guideline developer on August 15, 2011.

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